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(54) Title: CONTROLLING HEART RATE OR BLOOD PRESSURE IN PATIENTS CO-MEDICATED WITH PHOSPHODIESTERASE INHIBITORS FOR TREATMENT OF IMPOTENCE

(57) Abstract

The present invention provides a method for attenuating acute onset of heart rate or blood pressure increase in patients where the use of nitrate-containing drugs is contraindicated. Specifically disclosed are a method and a combination therapy for the control of heart rate or blood pressure during short term activities following administration of drugs such as sildenafil for treatment of impotence. The method comprises administration of beta-blockers, preferably rapid-acting beta blockers, such as (S)-(-)-ethyl 3-[2-[2-hydroxy-3-(isopropylamino) propoxy]phenyl]propionate hydrochloride at the onset of symptoms, at a pre-determined time before or following administration of sildenafil, or concomitantly with sildenafil or similar-acting anti-impotence agents.

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CONTROLLING HEART RATE OR BLOOD PRESSURE IN PATIENTS CO-MEDICATED WITH PHOSPHODIESTERASE INHIBITORS FOR TREATMENT OF IMPOTENCE

This application claims priority to U.S. Application No. 09/235,587, filed January 22, 1999, the entirety of which is incorporated by reference herein.

FIELD OF THE INVENTION

The present invention relates to a method for attenuating acute onset of heart rate or blood pressure increase in patients where the use of nitrate-containing drugs is contraindicated. In particular, the invention provides a method for the control of heart rate or blood pressure during short term activities following administration of drugs such as sildenafil for treatment of impotence.

BACKGROUND OF THE INVENTION

Various scientific articles and patent publications are referred to throughout the specification. These are incorporated by reference herein to describe the state of the art to which this invention pertains.

Viagra has become a popular oral therapy for the treatment of erectile dysfunction. Viagra is the citrate salt of sildenafil, chemically designated as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-methylpiperazine and is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Sexual stimulation causes the release of nitric oxide (NO) in the corpus cavernosum of the penis. NO activates guanylate cyclase, which elevates the levels of cyclic guanosine cyclase monophosphate (cGMP) to

smooth muscle relaxation in the corpus cavernosum and allow inflow of blood. PDE5 degrades cGMP in the corpus cavernosum. Sildenafil enhances the effect of NO by inhibiting PDE5, thus prolonging the elevated concentration of cGMP in the corpus cavernosum.

The physical and sexual activities likely to be engaged in by a patient after administration of sildenafil are activities that commonly cause increases in heart rate and blood pressure. Control of heart rate and blood pressure during these short-term activities is particularly important for patients at risk due to coronary artery disease, such as myocardial ischemic disorder. Severe attacks of chest pain, angina pectoris, occur when cardiac work and myocardial oxygen demand exceed the ability of the coronary arterial system to supply oxygen. The major determinants of myocardial oxygen consumption are heart rate and systolic tension (arterial pressure). Any increase in these determinants in the presence of reduced coronary blood flow may induce angina. The higher the blood pressure and the faster the heart rate, the greater the unmet myocardial oxygen need.

Attacks of angina are most commonly acutely prevented or treated by administration of the vasodilator, nitroglycerin (1,2,3-propanetriol trinitrate), in the form of a sublingual spray or tablet or chewable tablet. Nitroglycerin acts by relaxing the vascular smooth muscle, resulting in the dilation of peripheral arteries and veins, thereby promoting peripheral pooling of blood and decreasing the blood pressure around the heart.

Though nitroglycerin may be needed by a patient after administration of sildenafil, its use in conjunction with sildenafil is contraindicated. Consistent with its known effect on the NO/cGMP pathway as described above, sildenafil has been shown to

potentiate the hypotensive effects of nitrates. It is likely that sildenafil is inhibiting PDE5 in the smooth muscle of the vascular system as well as the corpus cavernosum, thus causing the observed potentiation of hypotension when taken in combination with other nitrate vasodilators, such as nitroglycerin.

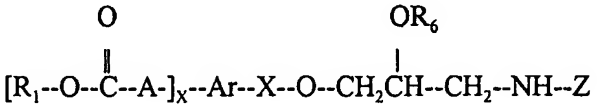
The increased hypotension caused by combined administration of sildenafil and nitrate vasodilators may have life-threatening consequences. Other symptoms of hypotension include headaches and vertigo. (PDR, 1994, p. 891). To avoid these deleterious results, a non-nitrate agent for prophylaxis or treatment of acute onset angina pectoris is needed for use in conjunction with sildenafil, in patients requiring medication for both the heart condition and impotence.

SUMMARY OF THE INVENTION

In accordance with the present invention, a method is provided for acutely treating or preventing angina, or other conditions arising from a sudden increase in heart rate or blood pressure, in patients requiring such treatment and who also are concurrently administered sildenafil or equivalent cGMP/NO pathway inhibitors. The method comprises administering to such patients a β-adrenergic receptor blocking agent or "beta-blocker" at specific time such that the therapeutic concentration of sildenafil and the beta-blocker coincide. The half life and bioavailability of commercially available beta-blockers after oral administration vary greatly (Goodman and Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition, P.1712- p.1792). Therefore the beta-blockers may be dosed up to 3 hours prior to the administration of oral sildenafil (or similar anti-impotence agent) or, in preferred embodiments as described below, along with or

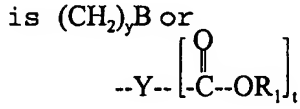
after administration of the anti-impotence agent. These "beta-blockers" may be administered by any commonly accepted routes such as orally, sublingually, intranasally or buccally.

A preferred embodiment of the present invention utilizes a rapid acting beta adrenergic receptor blocking agent ("beta-blocker") having Formula 1 below.

(1) 

wherein

X is a direct bond, $-CH_2$ or 

Z is $(CH_2)_yB$ or  ;

x is 0-3, y is 0-10; t is 0-3;

B, when y is 0, is lower alkyl, lower hydroxyalkyl, lower alkenyl, lower alkynyl or aralkyl;

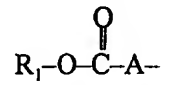
B, when y is 1-10, is $--NR_2COR_3$, $--NR_2CONR_3R_4$, $--NR_2SO_2R_3$, $--NR_2SO_2NR_3R_4$ or $--NR_2COOR_5$; wherein R_2, R_3, R_4 and R_5 may be the same or different and may be hydrogen, alkyl, alkoxyalkyl, alkoxyaryl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or aralkyl, except that R_3 and R_5 are not hydrogen when B is $--NR_2SO_2R_3$ or $--NR_2COOR_5$;

Y is C_1-C_6 straight or branched carbon chain, or aralkyl;

R_6 is hydrogen or -COJ wherein J is lower alkyl, wherein R_1 is lower alkyl, lower cycloalkyl, lower alkenyl, lower alky carboxymethyl, aryl carboxymethyl, aryl or aralkyl or C-4 to C-10 straight or branched carbon chain alkyl-cycloalkyl or a group -B-D, where B is C-2 to C-10 straight or branched carbon chain alkyl and D is hydroxy or alkyloxy or 2,3-dihydroxypropyl or 2,3-

dialkyloxypropyl or 2,2- dialkyl-1,3-dioxolane-5-methyl, where alkyl is C-1 to C-10 straight or branched carbon chain;

A is a direct bond, lower alkylene, or lower alkenylene; provided that when x is greater than 1, different occurrences of the

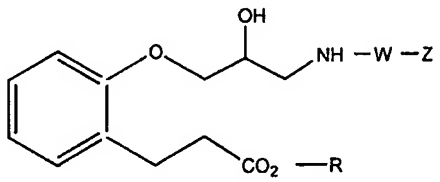


group may be the same or different;

Ar is heterocyclic, unsubstituted aromatic or aromatic substituted with lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, halogen, acetamido, amino, nitro, lower alkylamino, hydroxy, lower hydroxyalkyl or cyano, lower alkylcarbonyloxy, or pharmaceutically acceptable salts thereof.

A preferred sub-class of the compounds of Formula 1 above are represented by Formula 1A:

(1A)



wherein

R represents hydrogen or C-1 to C-10 straight or branched carbon chain alkyl or C-3 to C-6 cycloalkyl or C-4 to C-10 straight or branched carbon chain alkyl-cycloalkyl or a group -B-D, where B is C-2 to C-10 straight or branched carbon chain alkyl and D is hydroxy or alkyloxy or 2,3-dihydroxypropyl or 2,3-dialkyloxypropyl or 2,2- dialkyl-1,3-dioxolane-5-methyl, where alkyl is C-1 to C-10 straight or branched carbon chain;

W represents $CH(CH_3)CH_2$-, $C(CH_3)_2CH_2$-

Z represents hydrogen, $-NHCOR_2$, $-NHCONR_2R_3$ or $-NHSO_2R_2$ or $-NHSO_2NR_2R_3$ or $-NHCOOR_4$ wherein R_4 is alkyl of from 1 to about 6 carbon atoms, alkoxyalkyl wherein the alkyl groups may be the same or different and contain from 1 to about 6 carbon atoms, alkoxyaryl, cycloalkyl of from 3 to about 8 carbon atoms. R_2 and R_3 may be the same or different and represent hydrogen, alkyl of from 1 to about 6 carbon atoms, alkoxyalkyl wherein the alkyl groups may be the same or different and contain from 1 to about 6 carbon atoms, alkoxyaryl, cycloalkyl of from 3 to about 8 carbon atoms, a phenyl group substituted or unsubstituted, heteroaryl, furanyl, thiophenyl, imidazolyl, oxazolyl or indolyl or tetrahydrofuranyl, tetrahydropyranyl, dioxanyl, 2,2-dimethyl dioxolane-5-methyl, pyrrolidinyl, piperazinyl and tetrahydrooxazolyl, aralkyl except that R_2 and R_3 are not hydrogen when Z is -NHSO2R_2, or R_2 and R_3 may together with N form a 5 to 7 membered heterocyclic group; and pharmaceutically acceptable salts thereof.

Specifically preferred are ester compounds of Formula 1A, wherein W-Z represents isopropyl or t-butyl or Z represents $-NHCOR_2$, where R_2 is isopropyl, tetrahydro-furanyl, tetrahydropyranyl and $-NHCONR_2R_3$; wherein R_2 and R_3 together with N form a morpholino group and R is methyl, ethyl, n-propyl , cyclopropylmethyl, n-butyl, isobutyl or cyclopentyl.

In a preferred embodiment, the beta blocker is the compound *levo* SL-1050 hydrochloride ((S)-(-) ethyl 3-[2-[2-hydroxy-3-(isopropylamino) propoxy]-phenyl]propionate hydrochloride). In another preferred embodiment, the beta blocker is racemic ethyl 3-[2-[2-hydroxy-3-(isopropylamino) propoxy]-phenyl]propionate hydrochloride.

The agent preferably is administered sublingually, intranasally or orally, concomitantly with,

or at a pre-determined interval before or following administration of the sildenafil or equivalent therapeutic agent (hereinafter "anti-impotence agent"). Alternatively, the agent is administered sublingually or intranasally at the onset of symptoms of angina or abnormally increased heart rate or blood pressure.

In accordance with another aspect of the invention, a combination therapy of sildenafil or an equivalent anti-impotence therapeutic agent and the rapid acting beta-adrenergic receptor blocking agent is provided. In one embodiment, this combination therapy comprises a container containing separate appropriate dosages of the anti-impotence agent and the rapid acting beta-blocker, along with instructions for administration of the respective agents. In another embodiment, the combination therapy comprises a single pharmaceutical preparation for oral administration, containing both the anti-impotence agent and the rapid acting beta blocker.

Other features and advantages of the present invention will be better understood by reference to the detailed description that follows.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a combination therapy that enables safer use of sildenafil for patients with ischemic heart disease. The combination comprises a β-adrenergic receptor blocking agent ("beta-blocker"), preferably a composition represented by Formula 1 below and analogs or derivatives thereof (collectively referred to herein as "rapid-acting beta blockers"), in conjunction with sildenafil, to abort an angina episode or to prevent the occurrence of an angina episode, or to otherwise alleviate or prevent symptoms associated with sudden increases in blood pressure or heart rate. The use of these compounds in conjunction with sildenafil

provides the desired effect of controlling blood pressure and/or heart rate and accompanying symptoms, but will not potentiate the hypotensive effects of sildenafil. Accordingly, these rapid acting beta blockers are superior to nitroglycerin or other nitrate-containing vasodilators for treating patients co-medicated with sildenafil. It should be noted that, though sildenafil is exemplified herein, the present invention contemplates a combination therapy with any therapeutic agent for treatment of erectile dysfunction having the same mechanism of action as does sildenafil, i.e. selective inhibition of penis-specific PDE or other aspects of the NO/cGMP pathway that regulates penile erection.

Compounds of Formula 1, which, for convenience, is set forth in the section above, are described in detail in U.S. Patent No. 5,536,749 to Matier et al., which is incorporated by reference herein in its entirety. Each and every compound described in U.S. Patent No. 5,536,749 is contemplated for use in the present invention, including either stereomeric forms or racemic mixtures. A sub-class of Formula 1 preferred for use in the present invention is represented by Formula 1A set forth above. Specifically preferred for oral delivery are ester compounds of Formula 1A wherein W-Z represents isopropyl or t-butyl or Z represents $-NHCOR_2$, where R_2 is isopropyl, tetrahydro-furanyl, tetrahydropyranyl and $-NHCONR_2R_3$; wherein R_2 and R_3 together with N form a morpholino group and R is methyl, ethyl, n-propyl , cyclopropylmethyl, n-butyl, isobutyl or cyclopentyl. Ester compounds of Formula 1A are described in U.S. Patent Application Serial No. [ ], incorporated by reference herein in its entirety.

The class of compounds represented by Formula 1 is exemplified by the drug, *levo* SL-1050 hydrochloride ((S)-(-) ethyl 3-[2-[2-hydroxy-3-

(isopropylamino)propoxy]phenyl]-propionate hydrochloride). This compound also is an ester compound of Formula 1A. The use of *levo* SL-1050 HCl is a particularly preferred embodiment of the present invention.

Other beta-blockers suitable for use in the present invention include, but are not limited to: Betapace®, commercially available from Berlex Laboratories, Inc., Wayne, N.J.; Blocadren®, commercially available from Merck & Co, West Point, PA; Cartrol®, commercially available from Abbott Laboratories, Inc.,North Chicago, Il; Inderal®, commercially available from Wyeth-Ayerst Laboratories, Philadelphia, PA; Kerlone®, commercially available from G.D. Searle & Co., Chicago Il; Lopressor®, commercially available from Novartis Consumer Health, Inc., Summit, N.J.; and Zebeta®, commercially available from Lederle Laboratories, PearlRiver, N.Y. A list of other suitable β-adrenergic blocking agents is found in "USP Dictionary of USAN and International Drug Names" published by United States Pharmacopeial Convention, Inc. Rockville, MD 20852 under the heading: Anti-adrenergic and subheading: Beta-receptor.

Sildenafil is commercially available from Pfizer, Inc., New York, N.Y. Sildenafil and similar compounds also may be prepared by any suitable method known in the art. For instance, a process for the preparation of sildenafil is set forth in European Patent Application EP-A-0812845, published December 17, 1997, the entirety of which is incorporated by reference herein. Processes for preparing the general class of compounds exemplified by sildenafil are set forth in EP-A-0463756 and EP-A-0526004, both incorporated by reference herein in their entireties.

Pharmaceutical formulations comprising

sildenafil and similar compounds can be made according to standard procedures, e.g., as described in WO 94/28902, incorporated by reference herein in its entirety. Sildenafil preferably is formulated for oral administration as a tablet. However, sildenafil and similar compounds also may be formulated as a tablet, capsule or liquid for intranasal, buccal or sublingual delivery (see EP-A-0463756 and EP-A-0526004).

Levo SL-1050 hydrochloride is commercially available from Selectus Pharmaceuticals, Inc., Kennett Square, PA. This and similar compounds also may be prepared by any suitable method known in the art. For instance, processes for the preparation of compounds of Formula 1 are set forth in U.S. Patent No. 5,536,749 and U.S. Application Serial No. [ ] discussed above, and references cited therein, as well as 4,387,103, 4,692,446, 4,804,677, 4,810,717 and 4,959,390, the entireties of all of which are incorporated by reference herein.

Pharmaceutical formulations comprising compounds of Formula 1 can be made according to standard procedures, e.g., as described in U.S. Patent No. 5,536,749 and U.S. Application Serial No. [ ]. These preparations preferably are formulated as tablets, capsules or liquids for administration by a sublingual, buccal or intranasal route. They also may be formulated for oral administration, preferably as a rapidly-dissolving or controlled release tablet, as described in U.S. Application Serial No. 09/235,587, incorporated by reference herein.

Intranasal administration of beta blockers is described in U.S. Patent 4,428,883 issued January 31,1984; Pharmaceutical Research 3: 108-111, 1986; and U.S. Patent 5,242,949 issued September 7, 1993. The use of intranasal propranolol is reported as a beta

adrenergic agent is described in U.S. Patent 5,242,949 issued September 7, 1993 and Pharmaceutical Research 3: 108, 1986. Intranasal propranolol or any intranasal beta-adrenergic blocking agent can be administered so that the beta-blocking effect coincides with the effects of the anti-impotence agent.

In its most general form, the present invention provides a method for acutely treating or preventing angina, or other conditions arising from a sudden increase in heart rate or blood pressure, in patients requiring such treatment and who also are concurrently administered sildenafil or equivalent cGMP/NO pathway inhibitors. The method comprises administering to such patients a rapid acting beta blocker, as described above, either shortly before, concurrently with, or shortly after the administration of sildenafil, or on an as-needed basis following administration of sildenafil, while the drug remains in the patient's circulation. In either case, the respective drugs are administered as dosage units. The term "dosage units" refers to a physically discrete unit of the pharmaceutical preparation appropriate for the patient undergoing treatment. Each dosage unit contains a quantity of active ingredient calculated to produce the desired effect in association with the selected pharmaceutical carrier.

A preferred single dose of sildenafil is 25-100 mg for an adult human (Physicians Desk Reference 1998). Appropriate dosages of compounds similar to sildenafil may be determined by standard methods.

A single dose of a rapid-acting beta blocker having Formula 1 ranges from about 10 mg to about 500 mg, expressed as weight of the free base, for an adult human (approx. 70 kg). A preferred single dose of the active ingredient is about 25-500 mg. A preferred single dose

of the exemplary compound, *levo* SL-1050 HCl, is 50-200 mg. Appropriate dosages of specific compounds of Formula 1 may be determined by standard methods.

In one embodiment of the invention, the sildenafil (or similar anti-impotence agent) is administered, and the rapid-acting beta-blocker is administered on an as-needed basis thereafter, for at least as long as the anti-impotence agent remains in circulation. Preferably, the rapid-acting beta blocker is used exclusively as a replacement for nitrate-containing vasodilators by patients who regularly use a sildenafil-type of anti-impotence agent.

In another embodiment of the invention, the sildenafil-type anti-impotence agent and the rapid-acting beta blocker are administered together. Inasmuch as *levo* SL-1050 HCl and other compounds of Formula 1 have a duration of action of 2-4 hours, co-administration of the anti-impotence agent and the beta-blocker ensures control of blood pressure or heart rate during the time physical exertion and sexual activity are likely to be occurring. In a modification of this embodiment, the beta-blocker may be administered at a pre-determined time e. g., 30 minutes before or 1 hour following administration of the anti-impotence agent.

Dosage units of sildenafil or similar agents and the rapid-acting beta blocker can be formulated separately, but packaged together along with appropriate instructions, for convenience and ease of use. This embodiment is suitable for administration regimens in which the anti-impotence agent is taken separately, and the beta blocker is taken as needed, or at a pre-determined interval before or following administration of the anti-impotence agent.

Alternatively, sildenafil and the rapid-acting beta blocker can be formulated together into an

appropriate pharmaceutical preparation. This embodiment is suitable for an administration regimen in which the anti-impotence agent and the beta blocker are taken simultaneously. A preferred formulation comprising sildenafil and *levo* SL-1050 HCl is a powder or rapidly-dissolving tablet, formulated as follows:

Ingredients	**Range (% wt/wt)**	**Preferred Range (%wt/wt)**
levo SL-1050 HCl	10-40%	20-30%
Sildenafil	10-40%	20-30%
Lactose monohydrate	30-70%	40-50%
Crospovidone	5-18%	7-14%
Sodium bicarbonate	0-5%	2-4%
Magnesium Stearate	0.25-2.5%	0.5-1.0%
SiO_2	0-1.0%	0-0.5%

An appropriate amount of a sweetener(s) and/or a flavor(s) may be added if desired to mask an unpleasant taste, if any.

The (S)-Ethyl 3-[2-[2-hydroxy-3-(isopropylamino) propoxy]phenyl]propionate hydrochloride is mixed with the appropriate excipients until blend uniformity is achieved. This blend is packaged in appropriate size units in bottles, dosage container or powder paper for administration. Tablets are manufactured from the powder using conventional tableting equipment. The physical properties of the tablets preferably fall within the ranges shown below.

Test on the tablet	Range	Preferred range
Hardness in kp	2-5	2-3
Disintegration (min)	0.25-2.5	<1
70% Dissolution (min)	<2.0	0.5-5

The dissolution (USP 23 <711>) and disintegration test (USP 23 <701>) are performed according to USP methods.

The present invention is not limited to the embodiments described and exemplified above, but is capable of variation and modification without departure from the scope of the appended claims.

What is claimed:

1. A method of treating symptoms arising from increased heart rate or blood pressure in a patient in need of such treatment and wherein use of nitrate-containing drugs is contraindicated due to concurrent treatment of the patient with another pharmaceutical agent, the method comprising administering to the patient a beta adrenergic receptor blocking agent.

2. The method of claim 1, wherein the patient is concurrently being treated for erectile dysfunction by administration of an anti-impotence agent comprising a phosphodiesterase inhibitor.

3. The method of claim 2, wherein the phosphodiesterase inhibitor is sildenafil.

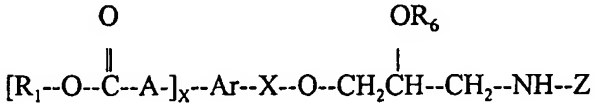
4. The method of claim 2, wherein the beta adrenergic receptor blocking agent is administered at a pre-determined time before, simultaneous with, or after administration of the anti-impotence agent.

5. The method of claim 1, wherein the beta adrenergic receptor blocking agent is administered by oral, sublingual, or intranasal dosing.

6. The method of claim 1, wherein the beta adrenergic receptor blocking agent is propranolol.

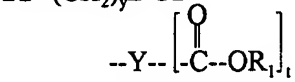
7. The method of claim 6, wherein the beta adrenergic receptor blocking agent is administered intranasally.

8. A method of treating symptoms arising from increased heart rate or blood pressure in a patient in need of such treatment and wherein use of nitrate-containing drugs is contraindicated due to concurrent treatment of the patient with another pharmaceutical agent, the method comprising administering to the patient a rapid acting beta adrenergic receptor blocking agent having a formula:

(1) 

wherein

X is a direct bond, $-CH_2$ or 

Z is $(CH_2)_yB$ or  ;

x is 0-3, y is 0-10; t is 0-3;

B, when y is 0, is lower alkyl, lower hydroxyalkyl, lower alkenyl, lower alkynyl or aralkyl;

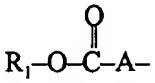
B, when y is 1-10, is $--NR_2COR_3$, $--NR_2CONR_3R_4$, $--NR_2SO_2R_3$, $--NR_2SO_2NR_3R_4$ or $--NR_2COOR_5$; wherein R_2, R_3, R_4 and R_5 may be the same or different and may be hydrogen, alkyl, alkoxyalkyl, alkoxyaryl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or aralkyl, except that R_3 and R_5 are not hydrogen when B is $--NR_2SO_2R_3$ or $--NR_2COOR_5$;

Y is C_1-C_6 straight or branched carbon chain, or aralkyl;

R_6 is hydrogen or -COJ wherein J is lower alkyl, wherein R_1 is lower alkyl, lower cycloalkyl, lower alkenyl, lower alky carboxymethyl, aryl carboxymethyl, aryl or aralkyl or C-4 to C-10 straight or branched carbon chain alkyl-cycloalkyl or a group -B-D, where B is C-2 to C-10 straight or branched carbon chain alkyl and D

is hydroxy or alkyloxy or 2,3-dihydroxypropyl or 2,3-dialkyloxypropyl or 2,2- dialkyl-1,3-dioxolane-5-methyl, where alkyl is C-1 to C-10 straight or branched carbon chain;

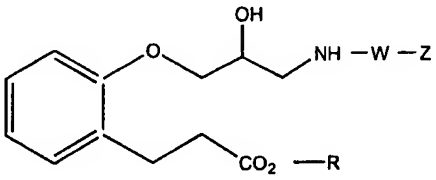
A is a direct bond, lower alkylene, or lower alkenylene; provided that when x is greater than 1, different occurrences of the



group may be the same or different;

Ar is heterocyclic, unsubstituted aromatic or aromatic substituted with lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, halogen, acetamido, amino, nitro, lower alkylamino, hydroxy, lower hydroxyalkyl or cyano, lower alkylcarbonyloxy, or pharmaceutically acceptable salts thereof.

9. The method of claim 8, wherein the rapid acting beta adrenergic receptor blocking agent comprises a formula:



Wherein

R represents hydrogen or C-1 to C-10 straight or branched carbon chain alkyl or C-3 to C-6 cycloalkyl or C-4 to C-10 straight or branched carbon chain alkyl-cycloalkyl or a group -B-D, where B is C-2 to C-10 straight or branched carbon chain alkyl and D is hydroxy or alkyloxy or 2,3-dihydroxypropyl or 2,3-dialkyloxypropyl or 2,2- dialkyl-1,3-dioxolane-5-methyl,

where alkyl is C-1 to C-10 straight or branched carbon chain;

W represents $CH(CH_3)CH_2$-, $C(CH_3)_2CH_2$-

Z represents hydrogen, -$NHCOR_2$, -$NHCONR_2R_3$ or -$NHSO_2R_2$ or -$NHSO_2NR_2R_3$ or -$NHCOOR_4$ wherein R_4 is alkyl of from 1 to about 6 carbon atoms, alkoxyalkyl wherein the alkyl groups may be the same or different and contain from 1 to about 6 carbon atoms, alkoxyaryl, cycloalkyl of from 3 to about 8 carbon atoms. R_2 and R_3 may be the same or different and represent hydrogen, alkyl of from 1 to about 6 carbon atoms, alkoxyalkyl wherein the alkyl groups may be the same or different and contain from 1 to about 6 carbon atoms, alkoxyaryl, cycloalkyl of from 3 to about 8 carbon atoms, a phenyl group substituted or unsubstituted, heteroaryl, furanyl, thiophenyl, imidazolyl, oxazolyl or indolyl or tetrahydrofuranyl, tetrahydropyranyl, dioxanyl, 2,2-dimethyl dioxolane-5-methyl, pyrrolidinyl, piperazinyl and tetrahydrooxazolyl, aralkyl except that R_2 and R_3 are not hydrogen when Z is -NHSO2R_2, or R_2 and R_3 may together with N form a 5 to 7 membered heterocyclic group; and pharmaceutically acceptable salts thereof.

10. The method of claim 9, in which the rapid-acting beta-adrenergic receptor blocking agent comprises an ester compound wherein W-Z represents isopropyl or t-butyl or Z represents -$NHCOR_2$, where R_2 is isopropyl, tetrahydrofuranyl, tetrahydropyranyl and -$NHCONR_2R_3$; wherein R_2 and R_3 together with N form a morpholino group and R is methyl, ethyl, n-propyl , cyclopropylmethyl, n-butyl, isobutyl or cyclopentyl.

11. The method of claim 8, wherein the beta adrenergic receptor blocking agent is (S)-(-) ethyl 3-[2-[2-hydroxy-3-(isopropylamino) propoxy]-phenyl]propionate hydrochloride.

12. The method of claim 8, wherein the beta adrenergic receptor blocking agent is racemic ethyl 3-[2-[2-hydroxy-3-(isopropylamino) propoxy]-phenyl]propionate hydrochloride.

13. The method of claim 8, wherein the beta adrenergic receptor blocking agent is administered at the onset of the symptoms.

14. The method of claim 8, wherein the patient is concurrently being treated for erectile dysfunction by administration of an anti-impotence agent comprising a phosphodiesterase inhibitor.

15. The method of claim 14, wherein the phosphodiesterase inhibitor is sildenafil.

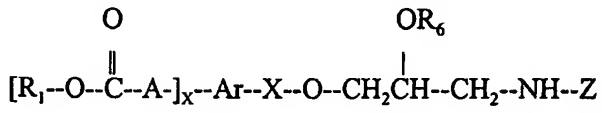
16. The method of claim 14, wherein the beta adrenergic receptor blocking agent is administered at a pre-determined time before or after administration of the anti-impotence agent.

17. The method of claim 14, wherein the beta adrenergic receptor blocking agent is administered simultaneously with the anti-impotence agent.

18. The method of claim 14, wherein the beta adrenergic receptor blocking agent is administered at the onset of the symptoms.

19. An article of manufacture for treating impotence and for controlling symptoms arising from increased blood pressure or heart rate, comprising a package containing:

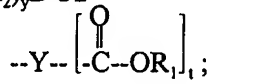
a) one or more dosage units of a rapid-acting beta adrenergic receptor blocking agent having a formula:

(1) 

wherein

X is a direct bond, $-CH_2$ or

Z is $(CH_2)_yB$ or



x is 0-3, y is 0-10; t is 0-3;

B, when y is 0, is lower alkyl, lower hydroxyalkyl, lower alkenyl, lower alkynyl or aralkyl;

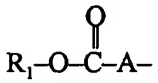
B, when y is 1-10, is $--NR_2COR_3$, $--NR_2CONR_3R_4$, $--NR_2SO_2R_3$, $--NR_2SO_2NR_3R_4$ or $--NR_2COOR_5$; wherein R_2, R_3, R_4 and R_5 may be the same or different and may be hydrogen, alkyl, alkoxyalkyl, alkoxyaryl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or aralkyl, except that R_3 and R_5 are not hydrogen when B is $--NR_2SO_2R_3$ or $--NR_2COOR_5$;

Y is C_1-C_6 straight or branched carbon chain, or aralkyl;

R_6 is hydrogen or -COJ wherein J is lower alkyl, wherein R_1 is lower alkyl, lower cycloalkyl, lower alkenyl, lower alky carboxymethyl, aryl carboxymethyl, aryl or aralkyl or C-4 to C-10 straight or branched carbon chain alkyl-cycloalkyl or a group -B-D, where B is C-2 to C-10 straight or branched carbon chain alkyl and D is hydroxy or alkyloxy or 2,3-dihydroxypropyl or 2,3-dialkyloxypropyl or 2,2- dialkyl-1,3-dioxolane-5-methyl, where alkyl is C-1 to C-10 straight or branched carbon chain;

A is a direct bond, lower alkylene, or lower alkenylene; provided that when x is greater than 1,

different occurrences of the

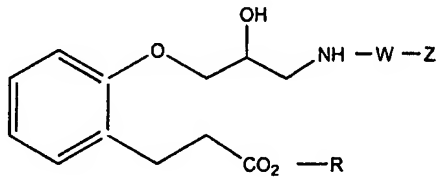


group may be the same or different;

Ar is heterocyclic, unsubstituted aromatic or aromatic substituted with lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, halogen, acetamido, amino, nitro, lower alkylamino, hydroxy, lower hydroxyalkyl or cyano, lower alkylcarbonyloxy, or pharmaceutically acceptable salts thereof; and

b) one or more dosage units of an anti-impotence agent comprising a phosphodiesterase inhibitor.

20. The article of manufacture of claim 19, wherein the rapid acting beta adrenergic receptor blocking agent comprises a formula:



Wherein

R represents hydrogen or C-1 to C-10 straight or branched carbon chain alkyl or C-3 to C-6 cycloalkyl or C-4 to C-10 straight or branched carbon chain alkyl-cycloalkyl or a group -B-D, where B is C-2 to C-10 straight or branched carbon chain alkyl and D is hydroxy or alkyloxy or 2,3-dihydroxypropyl or 2,3-dialkyloxypropyl or 2,2- dialkyl-1,3-dioxolane-5-methyl, where alkyl is C-1 to C-10 straight or branched carbon chain;

W represents $CH(CH_3)CH_2$-, $C(CH_3)_2CH_2$-

Z represents hydrogen, $-NHCOR_2$, $-NHCONR_2R_3$ or $-NHSO_2R_2$ or $-NHSO_2NR_2R_3$ or $-NHCOOR_4$ wherein R_4 is alkyl of from 1 to about 6 carbon atoms, alkoxyalkyl wherein the alkyl groups may be the same or different and contain from 1 to about 6 carbon atoms, alkoxyaryl, cycloalkyl of from 3 to about 8 carbon atoms. R_2 and R_3 may be the same or different and represent hydrogen, alkyl of from 1 to about 6 carbon atoms, alkoxyalkyl wherein the alkyl groups may be the same or different and contain from 1 to about 6 carbon atoms, alkoxyaryl, cycloalkyl of from 3 to about 8 carbon atoms, a phenyl group substituted or unsubstituted, heteroaryl, furanyl, thiophenyl, imidazolyl, oxazolyl or indolyl or tetrahydrofuranyl, tetrahydropyranyl, dioxanyl, 2,2-dimethyl dioxolane-5-methyl, pyrrolidinyl, piperazinyl and tetrahydrooxazolyl, aralkyl except that R_2 and R_3 are not hydrogen when Z is -NHSO2R_2, or R_2 and R_3 may together with N form a 5 to 7 membered heterocyclic group; and pharmaceutically acceptable salts thereof.

21. The article of manufacture of claim 20, in which the rapid-acting beta-adrenergic receptor blocking agent comprises an ester compound wherein W-Z represents isopropyl or t-butyl or Z represents $-NHCOR_2$, where R_2 is isopropyl, tetrahydrofuranyl, tetrahydropyranyl and $-NHCONR_2R_3$; wherein R_2 and R_3 together with N form a morpholino group and R is methyl, ethyl, n-propyl , cyclopropylmethyl, n-butyl, isobutyl or cyclopentyl.

22. The article of manufacture of claim 21, wherein the beta adrenergic receptor blocking agent is (S)-(-) ethyl 3-[2-[2-hydroxy-3-(isopropylamino) propoxy]-phenyl]propionate hydrochloride.

23. The article of manufacture of claim 21,

wherein the beta adrenergic receptor blocking agent is racemic ethyl 3-[2-[2-hydroxy-3-(isopropylamino) propoxy]-phenyl]propionate hydrochloride.

24. The article of manufacture of claim 19, wherein the anti-impotence agent is sildenafil.

25. The article of manufacture of claim 19, wherein the dosage units of the anti-impotence agent and the dosage units of the beta adrenergic receptor blocking agent are formulated for separate administration.

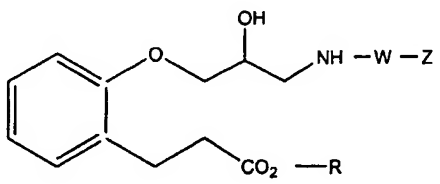
26. The article of manufacture of claim 19, wherein the dosage units of the anti-impotence agent and the dosage units of the beta adrenergic receptor blocking agent are formulated together.

27. The article of manufacture of claim 19, which further comprises instructions for administration of the dosage units.

28. A pharmaceutical preparation for treating impotence and for controlling symptoms arising from increased blood pressure or heart rate, which comprises effective amounts of:

a) an anti-impotence agent comprising a phosphodiesterase inhibitor; and

b) a rapid-acting beta adrenergic receptor blocking agent comprising an ester of a compound having a formula:



Wherein

R represents hydrogen or C-1 to C-10 straight or branched carbon chain alkyl or C-3 to C-6 cycloalkyl or C-4 to C-10 straight or branched carbon chain alkyl-cycloalkyl or a group -B-D, where B is C-2 to C-10 straight or branched carbon chain alkyl and D is hydroxy or alkyloxy or 2,3-dihydroxypropyl or 2,3-dialkyloxypropyl or 2,2- dialkyl-1,3-dioxolane-5-methyl, where alkyl is C-1 to C-10 straight or branched carbon chain;

W represents $CH(CH_3)CH_2$-, $C(CH_3)_2CH_2$-

Z represents hydrogen, $-NHCOR_2$, $-NHCONR_2R_3$ or $-NHSO_2R_2$ or $-NHSO_2NR_2R_3$ or $-NHCOOR_4$ wherein R_4 is alkyl of from 1 to about 6 carbon atoms, alkoxyalkyl wherein the alkyl groups may be the same or different and contain from 1 to about 6 carbon atoms, alkoxyaryl, cycloalkyl of from 3 to about 8 carbon atoms. R_2 and R_3 may be the same or different and represent hydrogen, alkyl of from 1 to about 6 carbon atoms, alkoxyalkyl wherein the alkyl groups may be the same or different and contain from 1 to about 6 carbon atoms, alkoxyaryl, cycloalkyl of from 3 to about 8 carbon atoms, a phenyl group substituted or unsubstituted, heteroaryl, furanyl, thiophenyl, imidazolyl, oxazolyl or indolyl or tetrahydrofuranyl, tetrahydropyranyl, dioxanyl, 2,2-dimethyl dioxolane-5-methyl, pyrrolidinyl, piperazinyl and tetrahydrooxazolyl, aralkyl except that R_2 and R_3 are not hydrogen when Z is -NHSO2R_2, or R_2 and R_3 may together with N form a 5 to 7 membered heterocyclic group; and pharmaceutically acceptable salts thereof.

29. The pharmaceutical preparation of claim 28, in which the rapid-acting beta-adrenergic receptor blocking agent comprises an ester compound wherein W-Z represents isopropyl or t-butyl or Z represents $-NHCOR_2$,

where R_2 is isopropyl, tetrahydrofuranyl, tetrahydropyranyl and $-NHCONR_2R_3$; wherein R_2 and R_3 together with N form a morpholino group and R is methyl, ethyl, n-propyl , cyclopropylmethyl, n-butyl, isobutyl or cyclopentyl.

30. The pharmaceutical preparation of claim 28, wherein the beta adrenergic receptor blocking agent is (S)-(-) ethyl 3-[2-[2-hydroxy-3-(isopropylamino) propoxy]-phenyl]propionate hydrochloride.

31. The pharmaceutical preparation of claim 28, wherein the beta adrenergic receptor blocking agent is racemic ethyl 3-[2-[2-hydroxy-3-(isopropylamino) propoxy]-phenyl]propionate hydrochloride.

32. The pharmaceutical preparation of claim 28, wherein the anti-impotence agent is sildenafil.

33. The pharmaceutical preparation of claim 28, which is formulated as a powder or tablet for oral administration.

34. A method of treating symptoms arising from increased heart rate or blood pressure in a patient in need of such treatment and wherein use of nitrate-containing drugs is contraindicated due to concurrent treatment of the patient with a phosphodiesterase anti-impotence agent, the method comprising administering to the patient a beta adrenergic receptor blocking agent under conditions whereby the therapeutic concentrations of the anti-impotence agent and the beta adrenergic receptor blocking agent coincide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/01284

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/50, 31/495, 31/535, 31/505, 31/445, 31/42, 31/415, 31/405, 31/38, 31/34, 31/235, 31/24
US CL : 514/253, 237.5, 256, 315, 376, 398, 415, 445, 473, 533, 534

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/253, 237.5, 256, 315, 376, 398, 415, 445, 473, 533, 534

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,536,749 A (MATIER et al.) 16 July 1996, see entire document, especially the abstract and columns 1 and 2.	1-34
Y	WO 94/28902 A1 (PFIZER LIMITED) 22 December 1994, see entire document, especially the abstract and pages 1, 2 and 17.	1-34

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 16 APRIL 2000	Date of mailing of the international search report 26 APR 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MINNA MOEZIE JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)★